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Review

# β-Blocker therapy in heart failure with preserved ejection fraction: Importance of dose and duration

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ABSTRACT

Heart failure is currently a social welfare and economic burden. In particular, the prevalence of heart failure with preserved ejection fraction (HFpEF) has increased and is currently equal to that of heart failure with reduced ejection fraction (HFrEF). Prognosis of HFrEF has improved in the past two decades, because many clinical studies have revealed the effectiveness of several pharmacological and non-pharmacological interventions for HFrEF patients, one of which is β-blockers. In contrast, there is no established therapeutic intervention to provide beneficial effects on HFpEF, and mortality and morbidity of HFpEF are currently as poor as those of HFrEF. This review will discuss β-blockers from a standpoint of therapeutic strategy for HFpEF.



**Contents**



## Introduction

Half of the patients with the clinical syndrome of heart failure (HF) in the community as well as those hospitalized for acute decompensated HF have preserved ejection fraction in the current era [1,2]. The incidence of HF increases with age, and the prevalence of HF is speculated to increase by 46% from 2012 to 2030 in the USA [3]. Patients with HF with preserved ejection fraction (HFpEF) are older and more often female compared to those with HF with reduced ejection fraction (HFrEF) [1], and such clinical characteristics of HFpEF lead to the continuous increase in its prevalence among HF patients [4].

The accumulated evidence about the effects of therapeutic interventions on HFrEF has resulted in the improvement of its prognosis, although not satisfactorily [5]. In contrast, there has been no established therapeutic strategy to be efficacious against HFpEF. Its prognosis has not changed over the past decades [5] and is currently as poor as that of HFrEF [5–7]. Therefore, it is an exigent issue to find out effective therapeutic intervention for HFpEF.

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## The effects of the inhibition of renin–angiotensin–aldosterone system in HFpEF

Previous clinical trials have demonstrated the beneficial effects of the inhibition of renin–angiotensin–aldosterone system (RAAS) in HFrEF, and its principal mechanism is to prevent structural remodeling such as myocardial hypertrophy and fibrosis. Myocardial hypertrophy and fibrosis are also observed in HFpEF patients [8,9] and are considered to play crucial roles in the development of signs and symptoms of HF. Our experimental studies have shown that the inhibition of RAAS provides beneficial effects on HFpEF model rats [10–13]. However, clinical trials to assess the effects of pharmacological RAAS inhibition on clinical outcomes of HFpEF (Table 1) have failed to reveal its benefits [14–17]. The discrepancy between experimental and clinical studies may be partly explained as follows. First, the experimental studies have assessed only the preventive effects of interventions, not therapeutic effects, because the administration of drugs was initiated after the development of left ventricular (LV) diastolic dysfunction but before the onset of HF. This may be supported by the subanalysis of I-Preserve trial that showed the beneficial effects of irbesartan in HFpEF patients with low, but not high, values of baseline plasma amino-terminal pro-brain natriuretic peptide [18]. Second, pathophysiology of HFpEF is heterogeneous, and the animal model only represents a part of HFpEF.

## The effects of β-blockers in HFpEF

It is well known that β-blockers significantly reduce mortality and morbidity of HFrEF patients, although the mechanisms of the benefits are not well clarified. Our clinical study showed that β-blockers improved LV diastolic function and symptoms of HFrEF patients even without changes in LV systolic function [19]. Therefore, its beneficial effects on HFpEF have been expected, and our's and other experimental studies demonstrated that the administration of β-blockers in the HFpEF model rats improved their survival rate [20,21]. In addition, the improvement in survival rate was dose-dependent (Fig. 1) [21].

In contrast to HFrEF, there have been only a few clinical trials to investigate the effects of β-blockers on HFpEF. The subanalysis of the SENIORS trial showed that the effects of nebivolol were similar between HF patients with EF> and ≤35% [22]. The SWEDIC study did not assess clinical outcomes but compared the changes in several Doppler echocardiographic indices of the transmitral and pulmonary venous flow velocity patterns such as *E*/*A* ratio, deceleration time of E wave, isovolumic relaxation time, and the ratio of systolic/diastolic pulmonary venous flow velocity between HFpEF patients treated with and without carvedilol. The SWEDIC study concluded that treatment with carvedilol resulted in a significant improvement in *E*/*A* ratio in patients with HF due to a LV relaxation abnormality [23]. However, these Doppler echocardiographic indices have many limitations for the assessment of LV diastolic function in subjects with preserved EF [24,25], and thus, it is difficult to make conclusive remarks based on the results of the SWEDIC study.

**Table 1**
Clinical trials to investigate the effects of pharmacological intervention except β-blocker on clinical outcomes of heart failure with preserved ejection fraction.

| Trial | Drug | Primary endpoint |
|---|---|---|
| DIG ancillary [50] | Digitalis | HF mortality or HF hospitalization |
| PEP-CHF [14] | ACEI | All-cause death or HF hospitalization |
| CHARM-Preserved [15] | ARB | CV death or HF hospitalization |
| I-Preserve [16] | ARB | All-cause death or CV hospitalization |
| TOP-CAT [17] | MRB | CV death, aborted cardiac arrest, or HF hospitalization |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; MRB, mineralocorticoid receptor blocker.

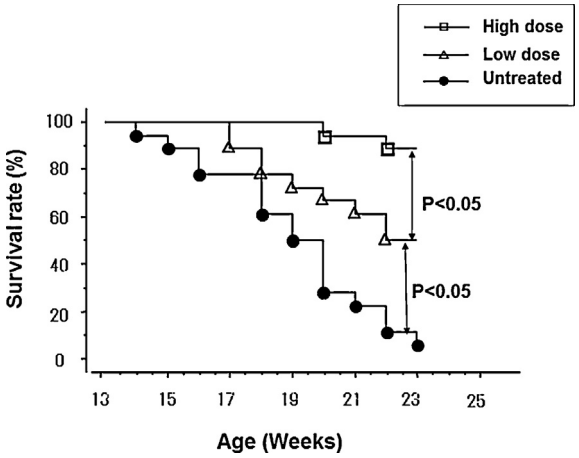


**Fig. 1.** Kaplan–Meier survival curves of the heart failure with preserved ejection fraction model rats of an untreated group, a group treated with low dose of bisoprolol (12.5 mg/kg/day) and a group treated with high dose of bisoprolol (250 mg/kg/day). The survival rate was improved by the administration of bisoprolol, and the effects of bisoprolol were dose-dependent.
Reproduced with permission from Nishio et al. [21].

Because of a lack of evidence about the effects of β-blockers on HFpEF, the J-DHF study was organized in Japan [26]. The number of the enrolled subjects was 245, and they were randomly divided into two groups treated with and without carvedilol. Mean age was 72 years, and 58% of the patients were men. The median follow-up period was 3.2 years, and there was no significant difference in the incidence of the primary endpoint (cardiovascular death or unplanned hospitalization for HF) and another composite endpoint (cardiovascular death or unplanned hospitalization for any cardiovascular causes) between the two groups. In Japan, the maximal dose of carvedilol allowed for the treatment of HFrEF in the insurance system is 20 mg/day, and the same dose was adopted as the target dose in J-DHF study. However, the median and mean prescribed doses were 7.5 and 8.5 mg/day, respectively. The underdose in the prescription of β-blockers for HFrEF patients is often observed in Japan as well as other western countries [27,28]. The J-DHF study was a prospective, randomized, open, blinded-endpoint design, and thus, the tendency to prescribe the low dose of β-blocker in the treatment of HFrEF might influence the actually prescribed dose of carvedilol in the subjects of the J-DHF study. Although not prespecified, the effects of the dose were assessed, and we found that the prescription of carvedilol more than 7.5 mg/day was associated with a significant reduction in the incidence of cardiovascular death or unplanned hospitalization for any cardiovascular causes (Fig. 2). Therefore, the results of the J-DHF study suggest that the standard dose prescription of carvedilol is effective in HFpEF.

Currently, there are no other prospective and randomized trials to investigate the effects of β-blockers on HFpEF, but the results of observational studies have been published. Several studies [29–36] as well as the meta-analysis of 12 previous studies [37] have reported that β-blockers provide beneficial effects on HFpEF (Fig. 3). In particular, the number of the subjects in three studies [30,32,36] was more than 10,000, and two studies [31,34] indicated the importance of the dose of β-blocker as the J-DHF study did. In contrast, some studies have concluded that β-blockers are not effective in HFpEF [38–42]. Although the OPTIMIZE-HF study [40] included 4153 patients, the number of the subjects in the other studies was less than 500. None of the five studies paid attention to the dose of β-blockers of the study subjects. If there is

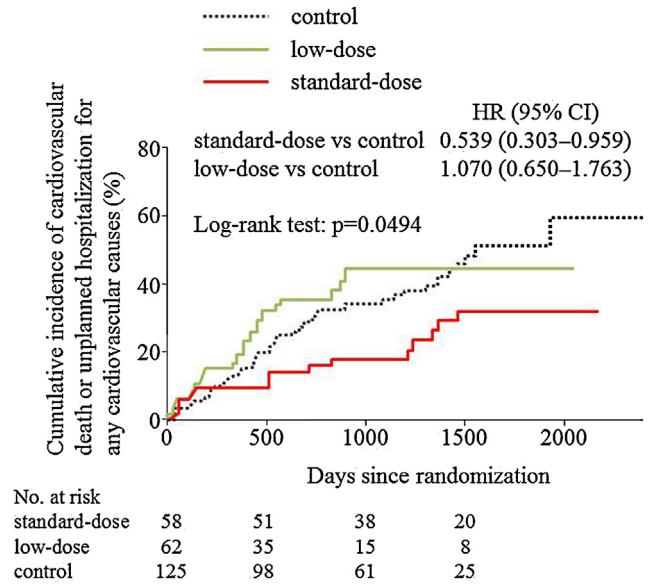


**Fig. 2.** Kaplan–Meier curves showing the time to first occurrence of the prespecified outcome, cardiovascular death or unplanned hospitalization for any cardiovascular causes. The carvedilol group was further divided into a group treated with carvedilol >7.5 mg/day ($n$ = 58, standard-dose group) and carvedilol ≤7.5 mg/day ($n$ = 62, low-dose group). Control group consists of heart failure with preserved ejection fraction patients treated without β-blocker. CI, confidence interval; HR, hazard ratio.
Reproduced with permission from Yamamoto et al. [26].

a dose dependency in the effects of β-blockers on HFpEF as the previous studies [26,31,34] have suggested, the conclusion about the effects of β-blockers on HFpEF in the observational studies is influenced by the patient characteristics. If the prevalence of patients treated with low dose, i.e. less than a half of the target dose, of β-blocker is high in the group treated with β-blockers, the incidence of clinical outcomes may not be different between groups treated with and without β-blockers. The HFrEF patients enrolled in the OPTIMIZE-HF study were treated with β-blockers at low doses [28]. It is plausible to speculate that the HFpEF patients of the OPTIMIZE-HF study were also treated with low doses of β-blockers, and that the absence of beneficial effects of β-blocker on HFpEF in the OPTIMIZE-HF study was at least partly explained by the underdose of β-blockers. Recently, further analysis of OPTIMIZE-HF concluded that the dose of β-blocker does not affect the clinical outcome in HFpEF patients [43]; however, the median follow-up was only 2.2 years. Shah et al. demonstrated that benefits of β-blockers emerged at follow-up for 3 years but not for 1 year in patients with HFpEF [32]. Thus, dose and duration of β-blocker therapy may be key determinants of the effects of β-blockers on clinical events in HFpEF patients.

## Heart rate in HFpEF

β-Blockers have a negative chronotropic action and are expected to reduce heart rate. An increase in heart rate in patients with HF is associated with the exacerbation of mortality, and thus, there has been a long controversy about whether the reduction in

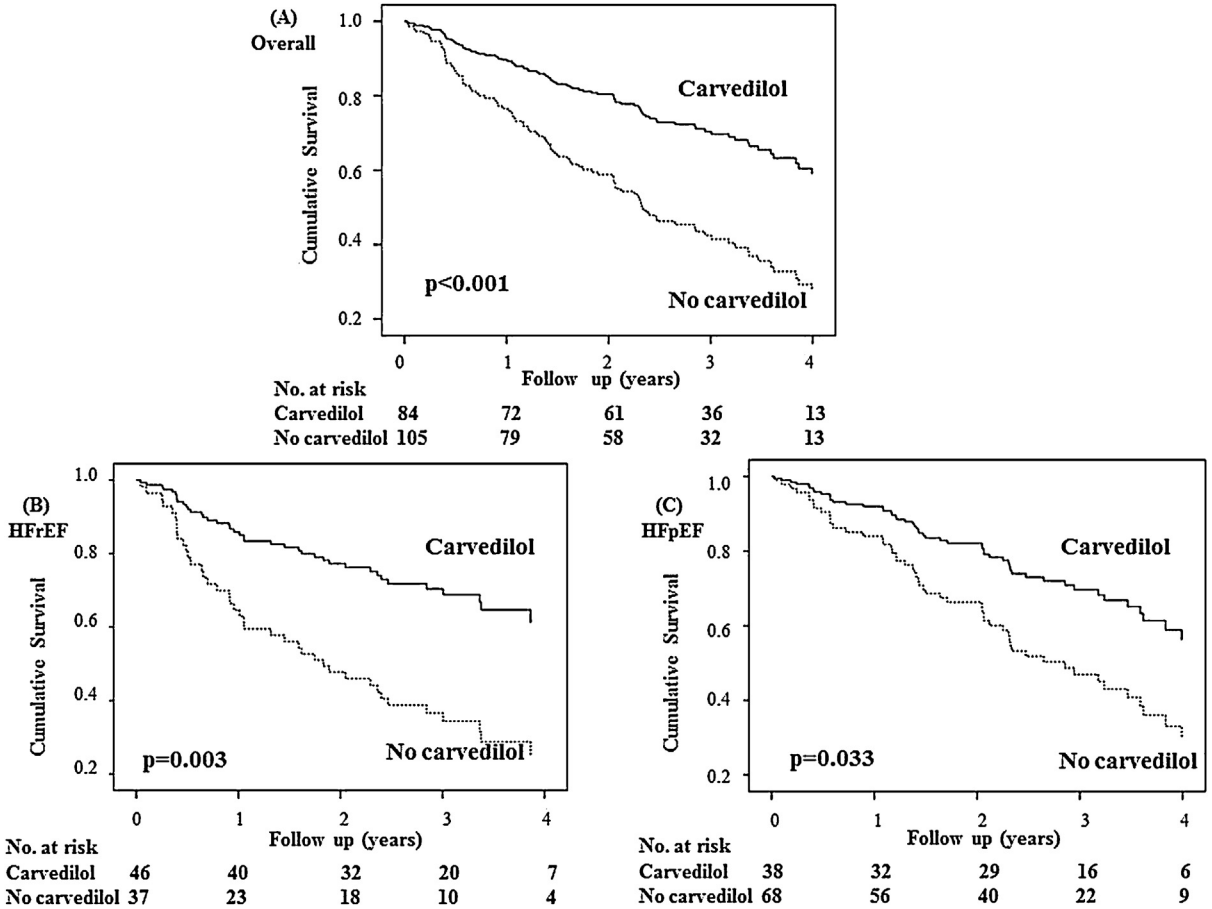


**Fig. 3.** Survival curves for all-cause mortality in HF patients treated with or without carvedilol at discharge. (A) Overall (HFrEF and HFpEF), (B) HFrEF, and (C) HFpEF, which were adjusted for age, sex, chronic obstructive pulmonary disease, and LV ejection fraction. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Reproduced with permission from Yanagihara et al. [35].

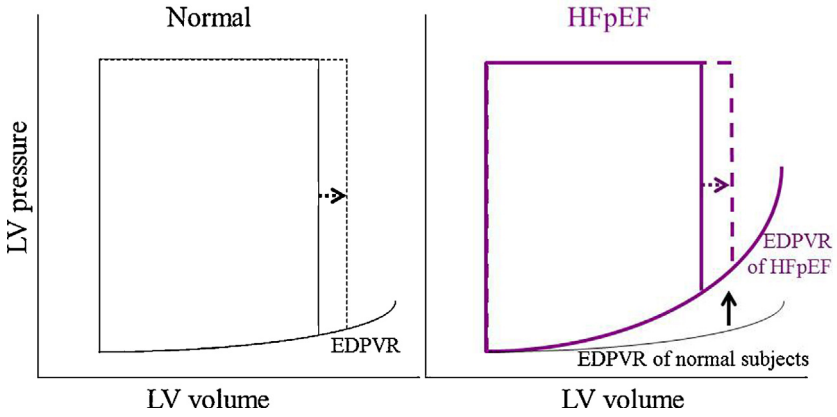


**Fig. 4.** Comparison of LV pressure–volume loop between normal and HFpEF subjects. The increase in LV end-diastolic volume (dotted line) results in the greater elevation of LV end-diastolic pressure in HFpEF because of the steeper end-diastolic pressure–volume curve. EDPVR, end-diastolic pressure–volume relation; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.

heart rate is a treatment target for HF. In patients with HFpEF, it is plausibly argued that the elevation of heart rate leads to the shortening of diastolic filling period and the consequent elevation of LV filling pressure. This is partly true; however, does the reduction of heart rate always result in the reduction in LV filling pressure? To keep cardiac output, the reduction in heart rate should be compensated by the increase in stroke volume. In patients with HFpEF, the slope of end-systolic pressure volume relation (end-systolic elastance) is high [44], and their contractile reserve is likely impaired. Therefore, the increase in end-diastolic volume is required to increase stroke volume following the law of Frank–Starling. As shown in Fig. 4, the slope of end-diastolic pressure–volume curve is steeper in HFpEF patients as compared to normal subjects. The increase in LV end-diastolic volume results in a greater elevation of LV end-diastolic pressure in HFpEF patients than in normal subjects, indicating that the reduction in heart rate does not necessarily lead to a decrease in LV filling pressure. Appropriate heart rate varies in HFpEF patients, and it is likely wrong to uniformly reduce heart rate in HFpEF patients.

## What is expected from β-blockers in HFpEF?

The beneficial effects of β-blockers in HFrEF are established. Although the administration of β-blockers in HFrEF results in the reduction of heart rate, the subanalysis of CIBIS II trial revealed that the beneficial effects of bisoprolol cannot be fully explained by the reduction in heart rate [45]. In fact, bucindolol significantly decreased heart rate in HFrEF patients, but did not improve clinical outcomes [46]. The mechanisms of the benefits of β-blockers in HFrEF are still to be established, and it is also unclear what we can expect from β-blockers in the treatment of HFpEF even if the results of the previous studies that showed beneficial effects of β-blockers, especially at high dose, on HFpEF are accepted.

Our experimental study [21] showed that the bisoprolol-induced dose-dependent improvement in survival rate of HFpEF model rats was provided through the combination of the prevention of LV hypertrophy and fibrosis, and that these effects were associated with the attenuation of LV stiffening in spite of the exacerbation of LV relaxation abnormality. The subanalysis of the J-DHF study [47] showed that the beneficial effects of a standard

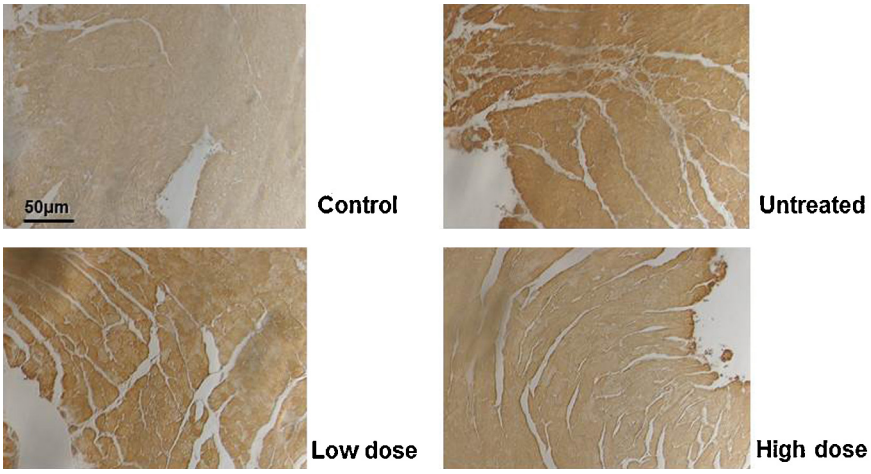


**Fig. 5.** Representative immunohistochemical staining for 4-hydroxy-2-nonenal (HNE) in the left ventricular tissue of a normotensive control rat (Control), a heart failure with preserved ejection fraction (HFpEF) model rat of an untreated group (Untreated), a HFpEF model rat of a group treated with low dose of bisoprolol (12.5 mg/kg/day, Low dose) and a group treated with high dose of bisoprolol (250 mg/kg/day, High dose). The administration of bisoprolol attenuated the HNE staining with the increase in the administered dose.
Reproduced with permission from Nishio et al. [21].

dose (≥a half of the target dose) of carvedilol were greater in patients with larger left atrial dimension, which suggests that carvedilol provides greater benefits in patients with advanced diastolic dysfunction.

The underlying mechanisms of such benefits remain to be clarified. Anti-inflammatory and anti-oxidative effects are likely common in β-blockers which are recommended for the treatment of HFrEF [48,49], and bisoprolol provided anti-inflammatory and anti-oxidative effects in association with the improvement in survival rate in the HFpEF model rat (Fig. 5) [21]. Thus, the suppression of inflammatory changes and oxidative stress may be one of the mechanisms of beneficial effects of β-blockers on cardiac structure and function.

## Conclusions

Currently, there is no established therapeutic intervention to improve the prognosis of HFpEF. One of the candidates is β-blocker treatment. The previous observational studies provided inconsistent conclusions about their effects on HFpEF; however, the absence of the benefits of β-blockers was drawn without taking into account the dose of β-blockers and/or the duration of the prescription. The long-term administration of standard doses of β-blockers may provide beneficial effects on HFpEF, and future studies are awaited to make a conclusive remark about the effects of β-blockers in HFpEF. However, a "one size fits all approach" as in previous clinical trials is likely inappropriate to find out an effective therapeutic strategy in HFpEF, because the pathophysiology of HFpEF is heterogeneous. Future clinical studies may be required to target a part of HFpEF with some specific characteristics.

## Conflict of interest

Dr Yamamoto reported receiving grant support and lecturer's fees from Daiichi-Sankyo Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co. Ltd., Takeda Pharmaceutical Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Boehringer Ingelheim Co. Ltd., Bristol-Myers Squibb Co. Ltd., and Toa Eiyo Ltd. for the past year.

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